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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,122	06/25/2001	Shohei Tanaka	Q64929	2326

7590 06/02/2003

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,122	TANAKA ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response to the Office action mailed December 18, 2003 filed March 18, 2003 is acknowledged. No amendment is submitted in the response filed March 18, 2003.

Claims 14-21 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isomura et al. (US Patent 4,990,503 from the Information Disclosure Statement received September 20, 2001) in view of Aparicio et al. (Leukemia, 1998;12:220-229 from the IDS received June 27, 2002) and Shipman et al. (British Journal of Haematology, 1997;98:665-672 from the IDS received September 20, 2001).

Isomura et al. teaches the heterocyclic bisphosphonic acid compounds, useful as bone resorption inhibitors, including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid can be blended with other pharmaceutically acceptable carrier to form medical composition suitable for oral administration (See particularly Col. 7, line 7-19; col. 9, example 5). Isomura et al. also teaches that 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid possess a strong bone resorption inhibition activities which can be used in diseases such as metastatic osteocarcinoma (See col. 6, line 4-66, particularly Table 1). Isomura et al. also teaches the oral dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to be useful in inhibiting bone resorption to be 1 to 1000mg daily (See col. 7, line 7-19).

Isomura et al. does not expressly teach 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid is useful in a method of inhibiting proliferation of myeloma cells. Isomura et al. does not expressly teach the effective dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to be 1 to 20 mg or 3 to 10 mg.

Aparicio et al. teaches two structurally different bisphosphonates: Aredia (pamidronate) and zoledronate, are effective in suppressing bone resorption and in inducing apoptosis in multiple myeloma cells by inducing apoptotic fragmentation (See the abstract; also page 223, col. 2, second paragraph). Aparicio et al. also teaches that both pamidronate and zoledronate are effective in inhibiting proliferation of multiple myeloma cells (See particularly page 226, col. 1, third paragraph).

Shipman et al. teaches three structurally different bisphosphonates: clodronate, pamidronate and YM 175, are effective in reducing the cell number of human myeloma cells (See page 667, Figure 1). Shipman et al. also teaches pamidronate and YM 175 as effective in inducing DNA fragmentation in myeloma cells (See page 668, col. 2, second paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid, in the herein claimed dosage, in a method of inhibiting proliferation of myeloma cells and/or suppressing bone resorption herein.

One of ordinary skill in the art would have been motivated to employ 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid, in the herein claimed dosage, in a method of both inhibiting proliferation of myeloma cells and/or suppressing bone resorption herein because various structurally distinct bisphosphonate compounds, pamidronate, zoledronate, clodronate, and YM 175, are known to be effective in inducing apoptosis in myeloma cells by inducing apoptotic fragmentation in myeloma cells. Possessing the teaching of the cited prior art, one of ordinary skill in the art would be reasonably expected to employ any known bisphosphonate compound, including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid, in the herein claimed method to inhibit the proliferation of myeloma cells and/or suppressing bone resorption. Furthermore, the optimization of result effect parameters (e.g., dosage range) is obvious as being within the skill of the artisan.

Response to Arguments

Applicant's arguments filed March 18, 2003 averring the cited prior art's failure to teach the dual effect (i.e., inhibiting multiple myeloma cells proliferation and suppressing bone resorption) of bisphosphonate have been considered, but are found persuasive. The cited prior art clearly teaches bisphosphonates, including the herein claimed bisphosphonate, are useful as cyotoxic and cytostatic to myeloma cells (See the teachings of Shipman et al. and Aparicio et al.). Moreover, they can suppress the bone resorption (See the teachings of Isomura et al. and Shipman et al.).

Applicant argues, in the response filed March 18, 2003, that the concentration of bisphosphonate for inducing apoptosis *in vivo* may not be achieved orally in the cited prior art. Applicant also argues that in view of Dallas, a reference of record provided by the applicant along with the response filed August 22, 2002, the peak serum concentration of bisphosphonate after oral administration will be about 10-fold less than the apoptosis inducing *in vitro* concentration of the same. These arguments have been carefully considered, but are not found persuasive. Examiner notes that in the Dallas article, the dosage administered to the mouse was 4μg, which produce a peak serum concentration of ibandronate of 5μmol/ml. In the instant case, the dosage is much higher than 4μg, and therefore, the almost 1000-fold increase of bisphosphonate dosage would be reasonably expected to increase the peak serum concentration to the apoptosis inducing concentration, absent evidence to the contrary. Furthermore, Examiner notes that not all the claims herein are reciting the route of oral administration and the dosage employed.

Applicant's arguments filed March 18, 2003 that the cited prior art's failure to teach the *in vivo* efficacy of bisphosphonate compounds in treating multiple myeloma have been considered; but are not found persuasive. Examiner notes that various structurally diverse bisphosphonate compounds are effective in inducing apoptosis in myeloma cells by inducing apoptotic fragmentation in myeloma cells. Moreover, the herein claimed compound is known to be useful as inhibitor of bone resorption. Please note that absolute expectation of success is not required for establishing *prima facie* obviousness rejection. Therefore, absent evidence to the contrary, employing these compounds, including the instant bisphosphonate compound herein, in the method of both inhibiting proliferation of myeloma cells and/or suppressing bone resorption would be reasonably expected to be effective.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
May 27, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER
6/1/03